ORIGINAL RESEARCH

Risk factors for head and neck cancer in the World Trade Center Health Program General Responder Cohort: results from a nested case–control study

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ABSTRACT

Objectives Head and neck cancers (HNCs) may be among the health consequences of involvement in the World Trade Center (WTC) response on and after 11 September 2001. We conducted a nested case–control study of WTC Health Program (WTCHP) general responders to examine the effects of WTC exposures and behavioural risk factors on HNC.

Methods We enrolled 64 cases and 136 controls, matched on age, sex and race/ethnicity within risk sets. We assessed tobacco and alcohol use, sexual activity, and occupational exposures prior to, during and after WTC exposure until case diagnosis via questionnaire. We obtained WTC exposure information (duration (first to last day), total days and location of work) from the WTCHP General Responder Data Center. We assessed associations with HNC, and interaction among exposures, using conditional logistic regression.

Results Responders in protective services versus other occupations had increased odds (OR: 2.51, 95% CI 1.09 to 5.82) of HNC. Among those in non-protective services occupations, arriving to the WTC effort on versus after 11 September 2001 was significantly associated with HNC (OR: 3.77, 95% CI 1.00 to 14.11). Duration of work was not significantly associated with HNC. Lifetime and post-WTC years of cigarette smoking and post-WTC number of sex partners were positively and significantly associated with HNC, while alcohol consumption was not.

Conclusions These findings suggest opportunities for HNC risk factor mitigation (eg, smoking cessation, human papillomavirus vaccination) and contribute to a risk factor profile which may assist WTCHP clinicians with identifying high-risk responders and improve detection and treatment outcomes in this population.

Key messages

What is already known about this subject?

- Health impacts for workers and volunteers who participated in the World Trade Center (WTC) response and recovery effort continue to accumulate, including reported excess cancer risk for all and specific cancer sites.
- A small but significant excess of head and neck cancer (HNC) has been observed among WTC Health Program General Responder Cohort members.

What are the new findings?

- To our knowledge, this is the first nested case–control study of cancer in a prospectively followed WTC cohort.
- Among WTC responders, HNC risk factors may include occupation in the protective services, arrival on site on September 11 rather than later, lifetime and post-WTC years of cigarette smoking, and higher number of sex partners after the WTC effort.
- However, in contrast to the general population, alcohol consumption was not associated with HNC.

How might this impact on policy or clinical practice in the foreseeable future?

- These findings contribute to the understanding of a potentially unique HNC risk factor profile among WTC responders, which may assist WTC Health Program clinicians with identifying high-risk responders and thus improve HNC detection and treatment outcomes in this population.

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INTRODUCTION

The collapse of the World Trade Center (WTC) buildings on 11 September 2001 (9/11) resulted in unprecedented local pollution that persisted for several months. Those involved in the WTC response efforts (ie, rescue, recovery and clean-up) were possibly exposed to multiple known and suspected human carcinogens.[1] A recent study of WTC Health Program (WTCHP) General Responder Cohort (GRC) members reported a 40% excess incidence (SIR 1.4, 95% CI 1.01 to 1.89) of head and neck cancers (HNCs) diagnosed between 2009 and 2012.[2] Additional research of WTC-exposed populations has observed excess incidence of all and other specific cancer sites, including prostate and thyroid.[3–5]

HNC in the general population is strongly associated with tobacco smoking, heavy alcohol

consumption and, for oropharyngeal cancers, persistent oral infection with oncogenic types of the human papillomavirus (HPV), usually HPV-16; in occupational settings, some HNCs have been associated with exposure to asbestos and wood, cement, and metal dusts.[6–12] Additionally, studies have reported interaction among occupational and behavioural risk factors in the risk of HNC,[13–15] and WTC responders' risk behaviours may have changed during or after the WTC response (eg, increased alcohol consumption, relapse to smoking). Therefore, the possible effects of WTC exposures on HNC risk may be direct, or mediated or moderated by population behavioural risk factors.

To assess the role of WTC exposure and behavioural risk factors in HNC risk, we conducted a case–control study nested within the WTCHP GRC, hypothesising that HNC occurrence is positively associated with intensity and duration of WTC exposure, tobacco smoking, alcohol consumption and sexual activity (a well-established indicator of HPV infection risk).[11]

METHODS

Study population

All study participants were WTCHP GRC members. The GRC is a longitudinal cohort formed since 9/11 supported by the US Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH) WTCHP.[16] To be eligible, responders must have worked or volunteered on the WTC response and met the exposure requirements. GRC members receive an initial physical examination and are eligible for annual health monitoring visits and treatment for WTC NIOSH-certified conditions. Monitoring visits include clinical examination and completion of questionnaires that a clinician reviews during the visit. The WTC General Responder Data Center (GRDC) in the Icahn School of Medicine at Mount Sinai in New York City maintains WTC-related exposure, clinical and questionnaire data from consented GRC members.

Case and control selection

We selected study participants among living GRC members who had previously consented to contact for WTC-related research studies. Eligible cases had HNC diagnosed between 2002 and 2016 (International Classification of Diseases (ICD)-9 codes 140–149.9, 160–161.0; ICD-10 codes C00.0-C14.9, C30-C32.9). We identified 94 eligible cases, and 64 (68.1%) consented to participate. For each enrolled case, we identified GRC members as potential controls using risk-set sampling, with risk sets defined as GRC members who were in the cohort when the case was diagnosed and had not yet attained the case's age at diagnosis. We matched potential controls on age, sex and race (non-Hispanic white vs other) within risk sets, and randomly selected up to eight. We enrolled 136 controls, with at least 2 for each case.

Questionnaire development

To inform questionnaire development, we reviewed standardised surveillance instruments (eg, National Health Interview Survey[17]) and questionnaires from other case–control studies of HNCs.[18 19] An expert panel including WTCHP GRC clinicians, survey methodologists, tobacco dependence specialists, oncologists, and occupational and cancer epidemiologists reviewed the questionnaire to assess face and content validity and cultural appropriateness. We evaluated the revised survey using cognitive interviewing procedures[20] in a convenience sample of nine GRC members (three with cancer) and three non-WTC-exposed persons with a history of cancer.

The final questionnaire included domains that assess the major population risk factors for HNC: tobacco use, alcohol use, marijuana use, sexual activity and exposure to environmental toxicants, including asbestos and dusts, during each of the three time periods: (1) before 9/11, (2) during involvement in the WTC response (except for environmental exposures, which the GRDC had previously collected), and (3) subsequently until the time of HNC diagnosis of the matched case.

Recruitment and data collection

Recruitment occurred from July 2017 to April 2018. Prospective participants were mailed letters inviting them to participate in the study, dubbed the World Trade Center Cancer Risk Epidemiology Study. The letter included information about the study and a telephone number and web address where respondents could schedule their telephone interview, elect to complete the survey online (offered because sequelae of HNC include speech impairments) or opt out of participation. Specially trained study interviewers attempted to contact potential participants and administer the questionnaire via telephone or encourage online completion.

WTC exposure measures

We obtained deidentified WTC exposure information for study participants via a data request to the WTCHP GRDC, including date of arrival, primary duty, duration of exposure and total number of days exposed. We defined date of arrival as a responder's first day of work on the WTC effort and categorised participants into three groups by arrival: (1) on 11 September 2001, (2) on 12 September 2001 or 13 September 2001, or (3) on or after 14 September 2001. We defined duration of exposure as the days from the first to the last day of work on the WTC effort, and total days of exposure as the number of days the responder was working on site. The WTCHP assessed primary work location as 'on the pile/in the pit', 'adjacent to the pile/pit', 'landfill', 'barges/loading piers' or 'elsewhere' during September 2001, October 2001, November through December 2001, and January through June 2002. We used a tiered approach, classifying work location into three levels: on the pile (spent the majority of at least one time period 'on the pile/in the pit'); adjacent to the pile (did not work on the pile but spent time adjacent to the pile/pit); and elsewhere (did not work on or adjacent to the pile).

Behavioural and occupational risk factor measures

We assessed tobacco smoking, alcohol consumption and number of sex partners (a surrogate for HPV infection[21]) for the three study periods (before, during and after WTC exposure). We selected years of tobacco smoking to estimate tobacco exposure, because increased HNC risk has been observed for long-term infrequent smokers[6] and because duration, separate from intensity, of smoking has been linked to smoking-related health risks.[22 23] We estimated lifetime years of cigarette smoking as the sum of smoking years during each time period.

We quantified the average alcohol consumption during each time period as the product of usual quantity per drinking occasion and usual frequency, converted to drinks per week.[24] Since duration of study time periods varied by participant, we multiplied this measure by the reported years of drinking during each period to estimate cumulative alcohol consumption as a function of quantity, frequency and duration of consumption. We summed across all three time periods to estimate lifetime cumulative alcohol consumption.

We assessed lifetime and period-specific number of sex partners using a question with categorical response options: *0*, *1*, *2–5*, *6–10*, *11–15*, *16–25*, *26–50*, *51–100*, or *more than 100*. Based on the distribution among cases, we classified participants into two groups for each of the study time periods: six or more partners versus fewer.

Previous occupation was related to WTC effort job functions,[25] and prior research has documented elevated HNC risk among certain occupational groups[26]; thus, we collected primary occupation outside the WTC response efforts via the survey. We classified participants into three groups for analysis: protective services workers (ie, law enforcement, non-New York City Fire Department [FDNY] firefighters, emergency services, military); construction, clean-up and machine workers; and other workers (include communications technicians).

Data analysis

We used conditional logistic regression to estimate the association between the explanatory variables and occurrence of HNC, accounting for the nested and matched design. Based on distribution among cases and model fit, we modelled primary work location as 'on the pile/pit' versus elsewhere, date of arrival as 'on 9/11' versus later, and occupation as 'protective services' versus other. We assessed the impact of variable inclusion and parameterisation using the likelihood ratio test for nested models. For standardised interpretation of continuous forms of tobacco and alcohol consumption in the context of study time periods of varying duration, we estimated the effects associated with an increase of 1 SD, based on the distribution among cases. We assessed interaction among WTC exposure variables and between WTC exposures and behavioural risk factors by including the respective cross-product term in the models, and examined stratified effect estimates when interaction was suggested by a p value less than 0.2. Regression analyses excluded 20 participants with missing data on explanatory variables.

We assessed potential bias from selection into the study by comparing demographic and exposure characteristics of enrolled and non-enrolled cases using χ^2 and t-tests for categorical and continuous variables, respectively.

We performed all analyses using SAS V.9.4.

RESULTS

Participant characteristics

As expected from the matched design, cases and controls were similar with respect to age and sex distribution; however, the control group was more racially diverse (34.6% non-white or Hispanic vs 17.2% of cases; table 1), so we adjusted for race/ethnicity in multivariable analyses. Among cases, the most commonly diagnosed HNC was oropharyngeal cancer (43.8%); 60.9% were employed in protective services occupations and 25.0% had ever served in the military; nearly half (49.2%) started on the WTC effort on 9/11. Compared with cases, fewer controls were employed in protective services (46.3%), had served in the military (16.2 %) and had started on the WTC effort on 9/11 (38.4%). The mean total days of work was similar for cases and controls, but the mean duration of work was longer for controls (117.9 vs 132.0 days).

During each of the study time periods (lifetime and before, during and after WTC exposure until case diagnosis), smoking prevalence and mean years of smoking were higher among cases (table 2). However, alcohol use (prevalence and cumulative consumption) was higher for controls. Prevalence of having six or more sex partners was higher for controls during the pre-WTC and during WTC exposure time periods but was higher for cases during the post-WTC period.

The mean duration of work was lowest for those who worked on the pile (mean±SD: duration, 118.6±96.8) and increased with distance from the WTC pile/pit (adjacent to the pile: 130.5±107.5; elsewhere: 139.8±108.3). Similarly, the mean total days of work for those who worked on the pile, adjacent to the pile and elsewhere was 64.5 (±64.9), 76.2 (±73.1) and 85.2

Table 1 Characteristics of cases and controls, WTC Cancer Risk Epidemiology Study

Characteristics	Cases (n=64)	Controls (n=136)
Demographics		
Age on September 11, mean±SD	41.9±6.8	41.6±6.8
Age at enrolment in WTCHP, mean±SD	51.1±9.1	46.8±7.5
Male sex, n (%)	57 (89.1)	120 (88.2)
Non-Hispanic white, n (%)*	53 (82.8)	89 (65.4)
Primary occupation, n (%)		
Protective services	39 (60.9)	63 (46.3)
Construction, clean-up, machines	9 (14.1)	33 (24.3)
Communications technicians, other	16 (25.0)	40 (29.4)
Ever served in military	16 (25.0)	22 (16.2)
WTC exposure measures		
Date of arrival on site, n (%)		
September 11	31 (49.2)	51 (38.4)
September 12–September 13	18 (28.6)	45 (33.8)
September 14 or later	14 (22.2)	37 (27.8)
Work location, n (%)		
On the pile/in the pit	26 (41.3)	49 (37.7)
Adjacent to pile/pit	25 (39.7)	60 (46.2)
Elsewhere	12 (19.1)	21 (16.2)
Duration of WTC work (first to last day), mean±SD	117.9±101.8	132.0±104.9
Total days worked/volunteered, mean±SD	72.7±77.5	72.6±69.5
Risk behaviours		
Smoking status, n (%)		
Current	5 (7.8)	10 (7.4)
Former	28 (43.8)	46 (33.8)
Never	31 (48.4)	80 (58.8)
Alcohol consumption, n (%)		
Current	36 (56.3)	102 (75.0)
Former	14 (21.9)	17 (12.5)
Never	14 (21.9)	17 (12.5)
Sexual behaviour history		
Age at sexual debut, mean±SD	17.4±2.6	16.6±2.9
Number of lifetime sex partners, n (%)		
1–5	24 (37.5)	36 (26.5)
6–10	18 (29.5)	37 (29.8)
11 or more	19 (31.2)	51 (41.1)
Ever diagnosed with a sexually transmitted infection, n (%)	6 (9.4)	17 (12.6)
Cancer information (cases only)		
Age at diagnosis, mean±SD	51.8±8.1	
Cancer site, n (%)		
Larynx	11 (17.2)	
Oral cavity†	13 (20.3)	
Oropharynx‡	28 (43.8)	
Other§	12 (18.8)	

Counts may not sum to group total due to item non-response.
*The race/ethnicity variable provided for matching used a since-revised classification that did not perfectly align with participants' reported race/ethnicity, shown here.
†Oral cavity includes tongue (C02), gum (C03), palate (C05), and other oral cavity and pharynx (C14).
‡Oropharynx includes base of tongue (C01), tonsil (C09) and oropharynx (C10).
§Other includes nasopharynx (C11), nasal cavity and middle ear (C30), accessory sinuses (C31), parotid gland (C07), and other major salivary glands (C08).
WTC, World Trade Center; WTCHP, WTC Health Program.

Table 2 Lifetime and pre-WTC, during WTC and post-WTC exposure behavioural risk factors among cases and controls, WTC Cancer Risk Epidemiology Study

Risk factor	Study group*	Lifetime, until case diagnosis	Prior to WTC exposure	During WTC exposure	After WTC exposure, until case diagnosis
Ever cigarette smoking, n (%)	Cases	33 (51.6)	33 (51.6)	16 (25.0)	19 (29.7)
	Controls	56 (41.2)	55 (40.4)	18 (13.2)	25 (18.4)
Years of cigarette smoking, mean±SD	Cases	10.5±12.7	8.5±9.9	0.1±0.2	1.9±3.8
	Controls	7.5±11.9	6.4±9.9	0.0±0.2	1.1±3.1
Pack-years of cigarette smoking, mean±SD†	Cases	6.4±10.1	5.2±8.1	0.0±0.1	1.1±2.7
	Controls	4.7±10.1	4.3±9.5	0.1±0.2	0.7±2.8
Ever alcohol consumption, n (%)	Cases	50 (78.1)	50 (78.1)	44 (68.8)	44 (68.8)
	Controls	119 (87.5)	117 (86.0)	108 (79.4)	110 (80.9)
Cumulative alcohol consumption,‡ mean±SD	Cases	149.4±288.0	110.3±212.2	1.3±3.2	39.5±98.6
	Controls	171.5±267.0	119.4±202.9	1.5±3.8	52.4±97.6
Drinks of alcohol per week, mean±SD	Cases	–	4.5±6.7	4.8±11.0	3.6±8.3
	Controls	–	4.9±6.7	4.2±7.5	5.3±9.2
6 or more sex partners, n (%)	Cases	37 (60.7)	32 (52.5)	§	15 (24.6)
	Controls	88 (71.0)	74 (59.2)	9 (7.1)	13 (10.2)

*Cases, n=64; controls, n=136.
†Pack-years of cigarette smoking was defined as (average number packs of cigarettes smoked per day) × (years of smoking).
‡Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of alcohol consumption).
§Cell counts <5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center.
WTC, World Trade Center.

(±84.7), respectively. These relationships were comparable for cases and control.

Multivariable analysis

Having a protective services occupation was significantly associated with a 2.5-fold increase in odds of HNC (OR: 2.51, 95% CI 1.09 to 5.82), adjusted for WTC exposure measures and lifetime risk behaviours; this association was similar when assessing effects from each study period (table 3). Arrival on 9/11 (vs later) was positively associated with HNC in all four models, while duration of WTC work was inversely associated with HNC, although these effects were moderate and not statistically significant. Work location (pile vs elsewhere) was not associated with HNC in any model.

Years of smoking was positively associated with HNC in all time periods, with the strongest associations observed when considering lifetime and post-WTC exposure smoking. For example, an increase of 1 SD lifetime years of smoking was associated with a 78% increase in odds of HNC (OR: 1.78, 95% CI 1.04 to 3.03). Cumulative alcohol consumption was not significantly associated with HNC in any model. Drinking and smoking can be highly correlated behaviours, so we conducted a sensitivity analysis removing smoking from all models and saw little difference in the estimated association between alcohol and HNC (online supplementary table 1). Lifetime number of sex partners was not significantly associated with HNC; however, having six or more sex partners (vs fewer) during the post-WTC exposure period was significantly associated with increased odds of HNC (OR: 2.92, 95% CI 1.15 to 7.46).

We observed interaction between work location and duration of work (table 4). Among those who did not work on the pile/pit, each 30-day increase in work duration was associated with an 18% decrease in odds of HNC (OR: 0.82, 95% CI 0.69 to 0.98), adjusted for other WTC exposures, occupation and lifetime risk behaviours, whereas this association was null among those who did work on the pile/pit (OR: 1.06, 95% CI 0.89 to 1.26). Additionally, results suggest that occupation may moderate the effect of arrival date (p for interaction=0.1616). Among those not in protective services occupations, arriving on 9/11 as opposed to later was associated with 3.77-fold increased odds (OR: 3.77, 95% CI 1.00 to 14.11) of HNC, adjusted for other WTC exposure measures and lifetime risk behaviours, as

Table 3 Multivariable associations of WTC-related exposures and behavioural risk factors with head and neck cancer, WTC Cancer Risk Epidemiology Study

	Model 1 Lifetime behaviours	Model 2 Pre-WTC exposure behaviours	Model 3 During WTC exposure behaviours	Model 4 Post-WTC exposure behaviours
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on September 11 (vs later)	1.85 (0.79 to 4.33)	1.64 (0.73 to 3.67)	1.47 (0.65 to 3.30)	1.77 (0.77 to 4.06)
Worked on pile/in pit (vs elsewhere)	1.24 (0.54 to 2.85)	1.15 (0.51 to 2.56)	1.41 (0.64 to 3.11)	1.25 (0.56 to 2.79)
Duration of WTC work,* per 30 days	0.92 (0.82 to 1.04)	0.93 (0.82 to 1.05)	0.92 (0.82 to 1.04)	0.94 (0.84 to 1.06)
Protective services occupation (vs other)	2.51 (1.09 to 5.82)	2.21 (0.99 to 4.96)	2.27 (1.00 to 5.14)	2.53 (1.10 to 5.83)
Years of cigarette smoking, per 1 SD	1.78 (1.04 to 3.03)	1.54 (0.95 to 2.49)	1.24 (1.00 to 1.56)	1.72 (1.04 to 2.85)
Cumulative alcohol consumption,† per 1 SD	0.68 (0.42 to 1.11)	0.78 (0.50 to 1.23)	1.02 (0.90 to 1.16)	0.76 (0.49 to 1.17)
6 or more sex partners (vs <6)	1.20 (0.50 to 2.86)	1.23 (0.57 to 2.65)	‡	2.92 (1.15 to 7.46)

SD, per case distribution. All models account for the matched design and are adjusted for race/ethnicity (non-Hispanic white vs other). All models include WTC exposures (arrival date, work location, duration of exposure) and occupational group. Model 1 includes lifetime behaviours (smoking, alcohol consumption, sex partners), model 2 includes pre-WTC exposure behaviours, model 3 includes behaviours during WTC exposure, and model 4 includes behaviours after WTC exposure until case diagnosis.
*Duration was defined as the number of days between the first and last day on site.
†Cumulative alcohol consumption was defined as (average number of drinks per week) × (years of consumption).
‡Cell counts <5 are suppressed per terms of the data use agreement with the WTC Health Program General Responder Data Center.
WTC, World Trade Center.

Table 4 Interaction of effects in modelling odds of head and neck cancer, WTC Cancer Risk Epidemiology Study

	Model 1 Lifetime behaviours	Model 2 Pre-WTC exposure behaviours	Model 3 During WTC exposure behaviours	Model 4 Post-WTC exposure behaviours
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Arrival on September 11 (vs later)*				
Among protective services	1.18 (0.42 to 3.33)	1.10 (0.40 to 3.00)	0.93 (0.35 to 2.50)	1.02 (0.37 to 2.85)
Among other occupations	3.77 (1.00 to 14.11)	3.02 (0.86 to 10.64)	3.26 (0.88 to 12.13)	4.43 (1.14 to 17.25)
Duration of work, per 30 days†				
Among those who worked on the pile/pit	1.06 (0.89 to 1.26)	1.05 (0.87 to 1.24)	1.01 (0.86 to 1.20)	1.04 (0.87 to 1.24)
Among those who worked elsewhere	0.82 (0.69 to 0.98)	0.84 (0.71 to 1.00)	0.85 (0.72 to 1.00)	0.87 (0.75 to 1.02)

All models account for the matched design.
*P value for interaction: model 1: 0.1616; model 2: 0.2078; model 3: 0.1257; model 4: 0.0813. Models adjusted for race/ethnicity (non-Hispanic white vs other), duration of work (first to last day), work location (on the pile/pit vs elsewhere), years of cigarette smoking (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively), cumulative alcohol consumption (average drinks per week × years of drinking) (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively), and number of sex partners (6 or more vs fewer than 6) (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively).
†P value for interaction: model 1: 0.0422; model 2: 0.0750; model 3: 0.1128; model 4: 0.1328. Models adjusted for race/ethnicity (non-Hispanic white vs other), date of arrival (on September 11 vs later), occupational group (protective services vs other), years of cigarette smoking (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively), cumulative alcohol consumption (average drinks per week × years of drinking) (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively), and number of sex partners (6 or more vs fewer than 6) (lifetime, pre-WTC, during WTC or post-WTC for models 1, 2, 3 or 4, respectively).
WTC, World Trade Center.

compared with the null association between arrival date and HNC among those in protective services (OR: 1.18, 95% CI 0.42 to 3.33). These findings were similar across all four models. We did not observe significant interactions between WTC exposures and any behavioural risk factors.

Compared with cases who were identified but not enrolled (n=38, including 8 deceased cases), study participants (n=64) were younger on 9/11 (mean±SD: 41.9±6.8 vs 45.9±10.6 years, p=0.0419) and a higher proportion were female (10.9% vs 0%, p=0.0346; table 5). Participants and non-participants did not significantly differ with respect to race/ethnicity or any of the WTC exposure measures used in this study.

Regression analyses excluding cases diagnosed prior to 2005 (n=4) yielded results similar to those reported in table 3 (online supplementary table 2). Substituting pack-years of smoking (ie, years of smoking times the average number of packs per day) in place of years of smoking in the main effect models did not substantively change the observed effects of WTC exposure or improve model fit, and pack-years of smoking during any study period was not significantly associated with HNC (online supplementary table 3). Substituting alternate measures of alcohol consumption (years of drinking, total binge drinking days) also yielded results similar to those presented in table 3, as did addition of survey mode, which was not significantly associated with HNC in any model (online supplementary tables 4–6).

Table 5 Comparison of demographic and WTC-related exposure characteristics between participating and non-participating cases, WTC Cancer Risk Epidemiology Study

Characteristics	Participating cases (n=64)	Non-participating cases (n=38)	P value*
Demographics			
Age on September 11, mean±SD	41.9±6.8	45.9±10.6	0.0419
Sex, n (%)			
Male	57 (89.1)	38 (100)	0.0346
Female	7 (10.9)	0 (0)	
Race, n (%)			
Non-Hispanic white	53 (82.8)	31 (83.8)	0.9000
Other	11 (17.2)	6 (16.2)	
WTC exposure measures			
Date of arrival on site, n (%)			
September 11	31 (49.2)	14 (37.8)	0.2699
September 12 or later	32 (50.8)	23 (62.2)	
Work location, n (%)			
On the pile/in the pit	26 (41.3)	13 (35.1)	0.5437
Elsewhere	37 (58.7)	24 (64.9)	
Duration of WTC work, mean±SD†	117.9±101.8	133.7±101.5	0.4627
Total days worked/volunteered, mean±SD ‡	72.7±77.5	59.3±61.7	0.3721

Counts may not sum to group total due to item non-response.
*χ^2 test for comparison of proportions or t-test for comparison of means.
†Duration was defined as the number of days between the first and last day on site.
‡Total days was defined as the actual number of days on site, excluding days not on site.
WTC, World Trade Center.

DISCUSSION

In light of a reported excess in HNC risk among WTC general responders,[2] we conducted a nested case–control study to identify risk factors for HNC in this population, including WTC exposures and risk behaviours before, during and after involvement in the WTC response. We observed that employment in protective services occupations, increased lifetime and post-WTC years of cigarette smoking, and having six or more sex partners during the post-WTC period were significantly associated with increased estimated risk for HNC. Additionally, arrival on 9/11 as opposed to later was strongly associated with increased estimated risk of HNC among those not in the protective services; however, contrary to our hypotheses, neither work location nor duration of work was positively associated with HNC.

Employment in the protective services was strongly associated with increased estimated risk of HNC; however, since epidemiological and mechanistic support for this observation outside this population is lacking, this association may reflect increased risk associated with job tasks specific to those in the protective services during the WTC efforts (eg, search and rescue[25]), perhaps through increased exposure to toxins. Other potential explanations include risk varying by phase of the WTC effort, other occupational exposures before and after the WTC response, or differences in socioeconomic position across occupational groups. Differential job tasks may also explain why arriving on 9/11 as opposed to later was associated with increased estimated risk of HNC only among those not employed in protective service occupations. A study of asthma outcomes among WTC-exposed persons reported that protective services workers were less likely than construction and public agency workers to have worn a mask or respirator on 9/11[25]; as such, differential use of personal protective equipment may not explain our observation, but may contribute to the overall risk observed for workers in the protective services.

Duration of work was inversely associated with HNC only for those who worked elsewhere on the WTC effort, suggesting a downward bias from a healthy worker survivor effect. If true, apparent lower risk among those who did not work on the pile could drive the non-significant inverse association observed between duration and HNC overall.

Years of tobacco smoking was significantly and positively associated with HNC, particularly when considering the post-WTC period. This finding is consistent with existing literature linking tobacco smoking to HNC and adds to the growing body of research implicating the importance of smoking duration in the risk of HNC.[6] In contrast, we did not observe a significant effect of smoking pack-years during the post-WTC period, suggesting that smoking even at lower levels following the WTC response carries elevated risk for HNC in this population. Previous studies have identified a positive association between post-traumatic stress disorder (PTSD) and smoking outcomes among WTCHP members.[27] Thus the observed effect of post-WTC smoking duration may reflect continued or relapse to smoking following the WTC response period, potentially mediated by PTSD. Taken together, targeted smoking cessation interventions for WTCHP responders may be important for mitigating risk for HNC, especially for those who suffer from PTSD.

Number of sex partners in the post-WTC period was significantly associated with increased odds of HNC. Prior research has found strong associations between increased sexual activity and both HPV infection and oropharyngeal cancer.[11 28–31] Oral HPV infection may contribute to HNC risk in WTC responders, suggesting that HPV prevention measures (eg, risk reduction education, vaccination) may benefit this population. In October 2018, the US Food and Drug Administration expanded the approved use of Gardasil 9 (a 9-valent recombinant HPV vaccine) to include women and men through age 45.[32] Since HPV vaccination has been shown to reduce vaccine-type oral HPV infection,[33] it should be encouraged among GRC members as indicated by age.

Although heavy alcohol consumption is a strong population risk factor for HNC,[8] we did not observe this association. This was surprising and may indicate under-reporting of drinking behaviours among cases, heavier drinking among GRC members relative to the general population or the presence of unmeasured alcohol-related comorbidities among study participants. This finding may also suggest a unique risk factor profile for this population, potentially because WTC exposure in general (not only at high levels) is an important factor in HNC aetiology. A comparison of WTC-exposed and general population (not WTC-exposed) cases may help shed light on this point. An additional consideration is that HPV-attributed oropharyngeal cancers tend to not be associated with tobacco or alcohol and appear to be aetiologically distinct from other types of HNC.[34] Indeed, a descriptive assessment of cases found that mean lifetime cumulative alcohol consumption varied substantially by cancer site group (364.8, 139.4, 54.4 and 78.1 for laryngeal, oropharyngeal, oral cavity and other cancers, respectively). Thus, it is possible that the lack of association with alcohol consumption reflects the presence of multiple heterogeneous causal pathways for HNC in this population.

This study is subject to several limitations. Despite the matched design, the small sample size yielded imprecise estimates and prevented cancer site-specific analyses, an important consideration given aetiologically distinct pathways for some sites and risk factors. As additional cases emerge in this population, future study may provide adequate power to perform site-specific analyses that can shed light on these questions.

Offering a web-based option for participation may have introduced a mode effect[35]; however, offering a non-verbal option was critical, given that common sequelae of HNC include impeded speech, and substantial care was taken to maximise similarities between survey modes. The interviewer-administered and self-administered surveys were identical with respect to text and supplemental information, and the interviewers were specially trained to avoid script deviations. A sensitivity analysis found no significant association between survey mode and HNC.

Our findings should be considered in light of potential biases, including self-selection into the WTCHP GRC, selection into this study, survivorship, measurement error, unmeasured confounding (eg, socioeconomic status, residential exposure to WTC dusts) and possible comorbidities not accounted for in the analysis. Although we found no differences in WTC-related exposures between cases enrolled and not enrolled in this study, participating cases were younger on average and more likely to be male. Since both WTC-related and behavioural exposures were self-reported, misclassification is possible; however, comprehensive survey development and cognitive testing of the instrument may have lessened the potential for differential recall.

A diagnosis of HNC can be devastating, particularly for WTC responders, many of whom endure PTSD due to their WTC-related experiences. The risk of treatment failure and death is high,[36] and many survivors suffer from persistent symptoms from the cancer or treatment.[37] There is no effective screening for HNC; however, our results contribute to the development of a risk factor profile for WTC responders that is potentially unique from that of the general population. This can assist WTCHP clinicians with identifying high-risk responders, which may in turn improve detection and treatment outcomes in WTC-exposed persons. Although this is a unique population, this research may inform risk detection among responders to other disasters, such as a building collapse following an earthquake, or wildfires, which have increased unprecedentedly in recent years due to climate change.

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